B. REMARKS

Upon entry of the present amendment, claims 15, 18 to 22 and 44 will be pending. For the Examiner's convenience, a marked up version of claim 15 showing the amendments is attached as Exhibit A. The amendment to claim 15 is supported, for example, by claims 15 and 16 as originally filed and, therefore, does not add new matter.

The grounds of rejection as set forth in the final Office Action mailed January 22, 2001 (Paper No. 7) and maintained in the Advisory Action mailed August 8, 2001 (Paper No. 11) are addressed below.

A. Regarding the Rejection under 35 U.S.C. § 101

The rejection of claims 15, 16, 18 to 22 and 44 under 35 U.S.C. § 101 as allegedly lacking utility, as set forth in the Office Action mailed January 22, 2001 ("final Office Action"), and maintained in the Advisory Action, respectfully is traversed.

It was maintained in the Advisory Action, for the reasons set forth in the final Office Action that the specification does not provide a specific substantial and credible utility because no correlation has been shown between the use of an antibody to detect GDF-12 and a liver disorder. It was stated in the final Office Action, for example, that the specification does not disclose a biological function of GDF-12, and there is no evidence or record or scientific rationale to support an associate of the claimed invention with a particular liver disorder

Claim 15 is directed to a method of detecting a liver cell proliferative disorder and claim 44 is directed to a method of detecting abnormal expression of GDF-12 in the liver of a subject. In general, the methods utilize an anti-GDF-12 antibody to detect GDF-12 in a specimen obtained from the subject, and compare the amount of GDF-12 detected in the sample with an amount in a control specimen, wherein a difference in the sample as compared to control is

indicative of a liver cell proliferative disorder (claims 15 and 18-22) and abnormal expression of GDF-12 (claim 44).

Applicants maintain that a method of detecting a cell proliferative disorder by determining an amount of a protein produced by cells involved in the disorder, including the disclosed method of detecting a liver cell proliferative disorder based on determining the amount of GDF-12, is a well established utility that is specific, substantial and credible. The utility is specific in that the specification discloses that GDF-12 is specifically expressed by liver cells and, therefore, provides a specific marker for liver cells (see, for example, Figure 1). The utility also is substantial in that there is a real world value in providing a means to determine whether an abnormal amount of liver cell proliferation is occurring in a subject, as can happen, for example, in a subject with a hepatoma or a hepatocarcinoma, or whether there is a disorder such as hepatitis, wherein damage to the liver is not repaired by liver cell proliferation. Furthermore, the utility is credible because one skilled in the art would believe, for example, that an increased level of liver cell proliferation would be associated with increased GDF-12 expression because more liver cells would be expected to produce more GDF-12.

By analogy, Applicants have previously pointed out that the levels of various proteins, including cyclin D1, PCNA, prothrombin, and others are known to correlate with the level of proliferation of cells producing these proteins and that the detection of such proteins has been used in diagnostic procedures. Further in this respect, Applicants have pointed out that the level of prostate-specific antigen (PSA) in the blood was well recognized as a diagnostic marker of a prostate cell proliferative disorder, even though the function of PSA was not known. Thus, even where the function of a protein such as PSA was not known, it was recognized that the level of PSA was increased above normal in benign prostate hyperplasia and in prostate carcinoma, presumably due, at least in part, to the increased number of prostate cells associated with these conditions and, therefore, that the levels of PSA can be indicative of a prostate cell proliferative disorder. Applicants submit that, similarly, in the present case, one skilled in the art, viewing the specification and having knowledge of the art, would have known, for example, that increased

levels of GDF-12 can be indicative of a liver cell proliferative disorder such as a hepatoma because GDF-12 is produced by liver cells and because increased levels of PSA, which is produced by prostate cells, is indicative of a prostate cell proliferative disorder.

In summary, it is submitted that the use of an antibody to determine the level of a protein, wherein the level of the protein is diagnostic of the proliferative state of cells that produce the protein, is a well established utility, which is specific, substantial and credible, and that, in view of the subject application and of knowledge in the art such as the use of PSA levels as indicative of a prostate cell proliferative disorder, one skilled in the art clearly would have recognized that an anti-GDF-12 antibody can be used to determine levels of GDF-12, which can be indicative of a liver cell proliferative disorder.. Accordingly, it is respectfully requested that the rejection of the claims under 35 U.S.C. § 101 be removed.

C. Rejections under 35 U.S.C. § 112

The objection to the specification and corresponding rejection of claims 15, 16, 18 to 22 and 44 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement respectfully are traversed.

For the reasons set forth above, it is submitted that the specification discloses a patentable utility, and it is further submitted that the specification teaches how to make and use an anti-GDF-12 antibody for purposes of practicing the claimed methods (pages 13, line 23, to page 16, line 2). As such, it is respectfully requested that this objection to the specification be withdrawn and that the corresponding rejection of the claims under 35 U.S.C. § 112, first paragraph, be removed.

In view of the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect respectfully is requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: December 20, 2001

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EXHIBIT A

MARKED UP VERSION OF CLAIM 1 SHOWING AMENDMENT

15. (Thrice amended) A method of detecting a liver cell proliferative disorder, comprising

contacting an antibody that specifically binds to growth differentiation factor-12 (GDF-12) polypeptide having an amino acid sequence as set forth in SEQ ID NO:12 with a liver specimen from a subject under conditions suitable for formation of a complex; and

comparing the amount of complex in the liver specimen to the amount in a control sample, wherein a difference is indicative of a liver cell proliferative disorder.